Oncotarget, 2016, vol.7, N39, pages 63065-63081

Targeted suppression of AR-V7 using PIP5K1α inhibitor overcomes enzalutamide resistance in prostate cancer cells

Sarwar M., Semenas J., Miftakhova R., Simoulis A., Robinson B., Wingren A., Mongan N., Heery D., Johnsson H., Abrahamsson P., Dizeyi N., Luo J., Persson J.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

One mechanism of resistance of prostate cancer (PCa) to enzalutamide (MDV3100) treatment is the increased expression of AR variants lacking the ligand binding-domain, the best characterized of which is AR-V7. We have previously reported that Phosphatidylinositol---phosphate 5-kinase alpha (PIP5Ka), is a lipid kinase that links to CDK1 and AR pathways. The discovery of PIP5Ka inhibitor highlight the potential of PIP5K1α as a drug target in PCa. In this study, we show that AR-V7 expression positively correlates with PIP5K1α in tumor specimens from PCa patients. Overexpression of AR-V7 increases PIP5K1α, promotes rapid growth of PCa in xenograft mice, whereas inhibition of PIP5K1α by its inhibitor ISA-2011B suppresses the growth and invasiveness of xenograft tumors overexpressing AR-V7. PIP5K1α is a key co-factor for both AR-V7 and AR, which are present as protein-protein complexes predominantly in the nucleus of PCa cells. In addition, PIP5K1α and CDK1 influence AR-V7 expression also through AKT-associated mechanism dependent on PTEN-status. ISA-2011B disrupts protein stabilization of AR-V7 which is dependent on PIP5K1α, leading to suppression of invasive growth of AR-V7-high tumors in xenograft mice. Our study suggests that combination of enzalutamide and PIP5K1α may have a significant impact on refining therapeutic strategies to circumvent resistance to antiandrogen therapies.

http://dx.doi.org/10.18632/oncotarget.11757

Keywords

AR-V7, Enzalutamide resistance, Lipid kinase inhibitor, PIP5K1α, Prostate cancer metastasis